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Veerle Coessens[a]; Krzysztof Matyjaszewski[a]
[a] Department of Chemistry, Carnegie Mellon University, Pittsburgh, PA, U.S.A.

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END GROUP TRANSFORMATION OF POLYMERS PREPARED BY ATRP, SUBSTITUTION TO AZIDES

VEERLE COESSENS and
KRZYSZTOF MATYJASZEWSKI*

Department of Chemistry
Carnegie Mellon University
4400 Fifth Avenue
Pittsburgh, PA, 15213

Key Words: Atom Transfer Radical Polymerization, End Group Functionalization, Azides

ABSTRACT

Polystyrenes, polyacrylates and poly(methyl methacrylate) prepared by atom transfer radical polymerization (ATRP) have predictable molecular weights, low polydispersities and well-defined halogen end groups. The halogen end groups have been substituted by other functionalities such as azides and amines. In order to predict the feasibility and selectivity of nucleophilic substitution reactions, the reactivities of the end groups of the different polymers were studied. First, model studies with benzyl halide (BzX), 1-phenylethyl halide (1-PEX), methyl 2-halopropionate (MXP), ethyl 2-bromoisobutyrate (EB*i*B) and 2-halopropionitrile (2-XPN) were performed. The models compounds were dissolved in DMF and after adding sodium azide (1.1 eq.), the reaction mixtures were stirred at 25°C. The relative magnitude of the rate constants for the reactions with the chlorinated

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* Author to whom correspondence should be addressed.

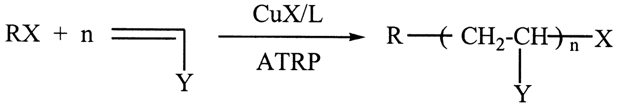
Fax : (412) 268-6897, E-mail: km3b+@andrew.cmu.edu.

substrates were found to be BzCl > MClP > 1-PECl ≈ 2-ClPN:22 > 6 > 1. Increased substitution at the carbon center decreased the rate of reaction, benzyl chloride reacted 22 times faster than 1-phenylethyl chloride. The brominated substrates reacted very fast. The rate constant of 1-PEBr, determined by competition experiments, was 4.5 times higher than the rate constant of benzyl chloride. Based on these results, the bromine end groups of different polymers were substituted under reaction conditions simular to those used for the model reactions. The end-functionalized polymers were characterized by ^{1}H-NMR, IR and MALDI-TOFMS.

INTRODUCTION

Atom transfer radical polymerization (ATRP) is one of the most effective methods to control radical polymerizations [1-3]. Several vinyl monomers such as styrenes, acrylates, methacrylates, and acrylonitrile have been polymerized in a broad molecular weight range yielding polymers with molecular weights predetermined by the $\Delta[M]/[I]_0$ ratio and with low polydispersities [4-5]. The end groups of the polymers are defined by the structure of the initiator used. As shown in Scheme 1, the alkyl group of the alkyl halide initiator remains at one end of the produced polymer chain, a halogen atom is quantitatively transferred to the other end of the chain.

The halogen end group can be converted to other functional groups using standard organic procedures. However, the transformation is preferably carried out under mild conditions, as the substitution must be as free of side reactions as possible and the yield of the transformation reaction must be quanti-tative. The functionalized polymers can find many applications, for example as macromonomers, telechelics or other specialty polymers. Azides are interesting end functional groups because they can be converted to amino end groups [6]. In this article, the kinetics of the replacement of the halogen end groups by azides is described. First, model studies were performed to study the reactivity of the



Scheme 1. The synthesis of polymers by atom transfer radical polymerization (ATRP).

different polymer end groups. The compounds 1-phenylethyl halide, methyl 2-halopropionate, ethyl 2-bromoisobutyrate and 2-halo-propionitrile were used as models for the end groups of respectively polystyrenes, polyacrylates, polymethacrylates and polyacrylonitrile. Upon reaction with sodium azide, the reactivities of the brominated and the chlorinated substrates were compared. All reactions were performed in dimethylformamide because of the poor solubility of sodium azide in other organic solvents. Guidelines for the rates of the reactions between organic halides and nucleophiles were found in several earlier publications [7-10]. However, experimental conditions have an important effect on the rate of the nucleophilic displacement reactions. The solvent, for example, plays a major role not only in the magnitude of rate constants, but also in orders of nucleophilic reactivity [11]. Therefore, model studies were performed using reaction conditions, applicable to polymeric substrates.

Then, low molecular weight polymers were prepared by ATRP and the polymeric halogen end groups were substituted by azides under reaction conditions, similar to those used for the model studies.

The analytical procedures used to follow the transformation of the end groups included GC (model studies), ^{1}H-NMR, IR and MALDI-TOFMS.

EXPERIMENTAL

Materials

Methyl acrylate was purified by distillation, styrene was filtered through alumina. CuBr was purified by stirring in acetic acid, washing with methanol, then drying. All other reagents, purchased from Aldrich or Acros, were used as received.

Analysis

GPC measurements were carried out using a Waters 510 liquid chromatography pump equipped with four Phenogel columns (100Å, 1000Å, linear and guard) in series with a Waters 410 differential refractometer. A 300 MHz Brüker NMR spectrometer was used for H-NMR analysis. GC measurement were carried out using a Shimadzu GC-14A equipped with a wide-bore capillary column (J&W Scientific, DB-WAX). An ATI Mattson Infinity FT-IR spectrometer was used for IR analysis. MALDI-TOFMS-spectra were obtained using a PerSeptive Biosystems Voyager Elite instrument, equipped with a N_2 laser at 337 nm.

Model Studies

To a 1 M solution of substrate (substrates were benzyl halide, 1-phenylethyl halide, methyl 2-halopropionate, methyl 2-halopropionitrile or ethyl 2-bromoisobutyrate; halides were chlorides or bromides) in dimethylformamide, sodium azide (1.1 eq.) was added and the reaction mixture was stirred at 25°C. Samples for GC-analysis were taken at regular time intervals. Analysis of the ^{1}H-NMR spectra of the resulting products are given in the section 'Results and Discussion'.

Preparation of Poly(methyl acrylate)

Methyl acrylate (5 ml, 55.5 mmol), 2,2'-dipyridyl (bipy, 514 mg, 3.3 mmol), CuBr (15.7 mg, 1.1 mmol), methyl 2-bromopropionate (0.3 ml, 2.6 mmol), and ethylene carbonate (5 g) were stirred for 2 hours at 90°C. THF was added and the mixture was passed through alumina. The polymer was then precipitated in n-hexanes.

Preparation of Polystyrene

See 'Preparation of Poly(methyl acrylate)' except that as solvent 1,4-dimethoxybenzene was used, 1-phenylethyl bromide was used as initiator, the reaction temperature was 110°C and the resulting polymer was precipitated in methanol.

Reaction of the Polymer End Groups with Sodium Azide

To a 0.05 M solution of polymer in dimethylformamide, sodium azide (1.1 eq. towards the end groups) was added. After 12 hours stirring at room temperature, the polymers were purified by extraction (water/chloroform). The organic phase was dried with $MgSO_4$ and evaporated.

The analysis of the end groups is described in 'Results and Discussion'.

RESULTS AND DISCUSSION

The substitution of the halogen end groups by azides has been reported previously by our group [12]. Bromine terminated polyacrylates or polystyrene were treated in dry tetrahydrofuran with tetrabutylammonium fluoride (TBAF) and trimethylsilyl azide (Me_3SiN_3) yielding azide terminated polymers.

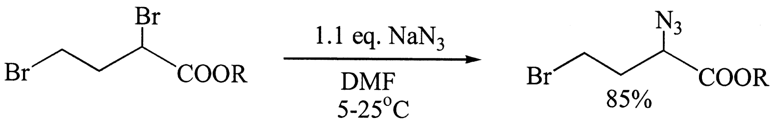
However, trimethylsilyl azide is hydrolytically unstable and an alternative displacement process was considered.

A more convenient method and in organic synthesis the most commonly applied route to obtain alkyl azides is the displacement of halides by azide ions [13]. With alkali metal azides such as sodium azide the reaction is performed in a polar solvent (typically dimethylformamide) to homogenize the reaction mixture.

According to model studies, bromo-terminated polyacrylates should be good substrates for the nucleophilic substitution of the halogen end group by azide [14]. As shown in Scheme 2, the electron-withdrawing effect of the ester function favors the chemoselective displacement of the halide at that reaction site under mild reaction conditions.

In an attempt to ascertain the reactivity of the end groups of the different polymers synthesized by ATRP, model compounds were reacted with sodium azide in DMF solutions. 1-Phenylethyl halide was used as a model for polystyrene, methyl 2-halopropionate for polyacrylates, ethyl 2-bromoisobutyrate for polymethacrylates and 2-halopropionitrile for polyacrylonitrile. Chlorides and bromides were used as halides. The model reactions were performed with a 1 M substrate concentration in DMF and with 1.1 equivalent of sodium azide. The reaction mixtures were stirred at 25°C and the conversion was followed using GC-analysis.

In Figure 1, the results of the reactions for the polyacrylate model systems are shown. The reaction of methyl 2-bromopropionate with sodium azide occurred almost instantaneously, with methyl 2-chloropropionate the reaction proceeded somewhat slower (50% conversion after 50 minutes). The reaction with ethyl 2-bromoisobutyrate, although at a tertiary carbon center, proceeded in a comparable rate as the reaction with methyl 2-chloropropionate. The fairly good reactivity of this compound is certainly due to a combination of the good leaving group ability of the bromine end group and the activating presence of the ester. The powerful activating effect of carbonyl groups and other related groups was explained by Bordwell as a combination of a rate-enhancing inductive effect and the absence of rate-retarding steric effect [10]. In Figure 2, the results for the models of polystyrene are presented. Again, it was observed that the sub-



Scheme 2. The selectivity in the reaction of a dibromo ester with sodium azide[14].

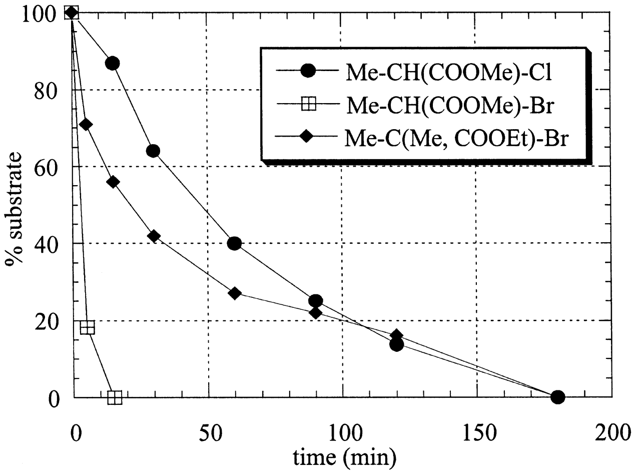


Figure 1. Kinetics of the reaction of methyl 2-halopropionate or ethyl 2-isobutyrate (1 M in DMF) with sodium azide (1.1 eq.) at 25°C.

strate with the bromine leaving group reacted almost instantaneously, the chlorinated substrate reacted quite slow (50% reacted after 4 hours). In Figure 3, the model system for polyacrylonitrile is shown. The same pattern was observed, the chlorinated substrate reacted much slower than the brominated one.

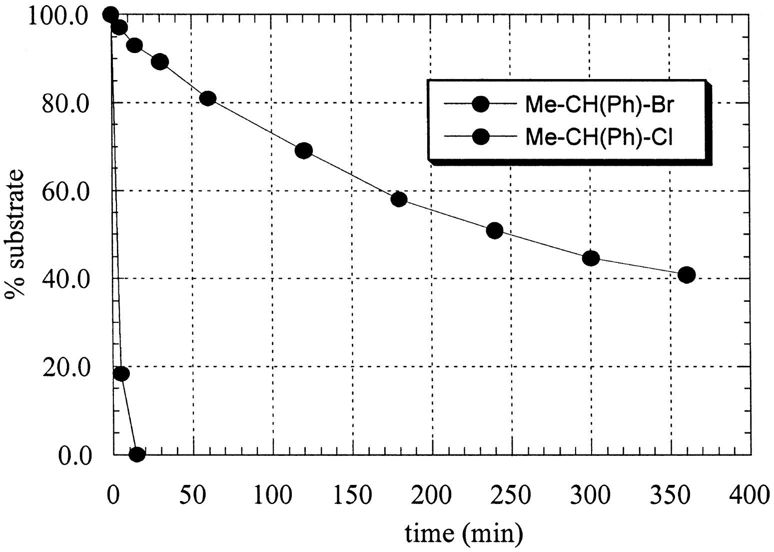


Figure 2. Kinetics of the reaction of 1-phenylethyl halides (1 M in DMF) with sodium azide (1.1 eq.) at 25°C.

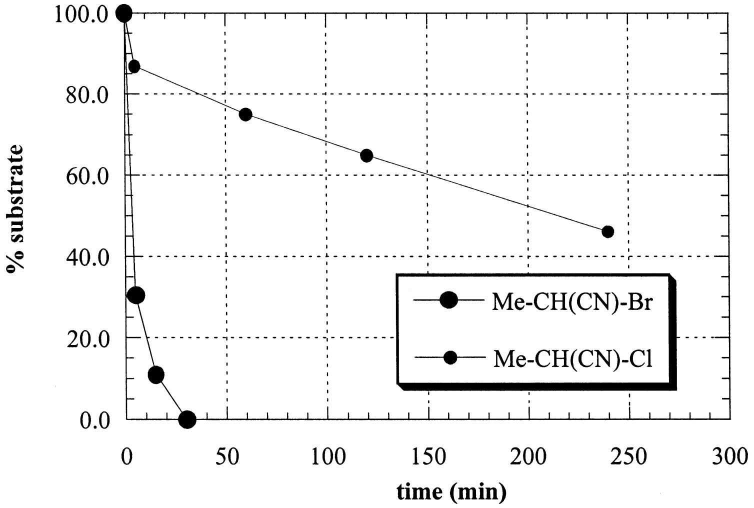


Figure 3. Kinetics of the reaction of 2-halopropionitrile (1 M in DMF) with sodium azide (1.1 eq.) at 25°C.

For the chlorinated substrates and ethyl 2-bromoisobutyrate, the rate constants of the reactions were calculated, assuming that in the model reactions (1 M substrate concentration in dimethylformamide) the initial concentrations of substrate and sodium azide were comparable [15]. As the kinetics showed deviation from second-order behavior at higher conversions (conversion > 40%), the initial slopes of the second-order plots were used to calculate the rate constants.

The data listed in Table 1 indicated that the order of reactivity of the chlorinated substrates was BzCl > MClP > 1-PECl (2-ClPN, the relative magnitude of the rate constants being 21 > 6 > 1. Nucleophilic substitution reactions occur faster at primary carbon centers (BzCl), however, the reactivity of a secondary carbon center is increased by the electron withdrawing effect of an ester group (MClP). The latter effect was also observed for the brominated substrates. When 1-phenylethyl bromide, methyl 2-bromopropionate and sodium azide were dissolved in DMF in a 1/1/1 ratio, 75% of the propionate and 25% of the 1-phenylethyl bromide was consumed.

Under the experimental conditions used, 1 M substrate concentration in DMF, the reactions with the brominated substrates occurred very fast. In order to estimate the rate constants, competition experiments were performed and alternatively the concentrations of 1-phenylethyl bromide and sodium azide were lowered fifty times (0.02 M concentration in DMF). The competition experi-

TABLE 1. Rate Constants for the Reactions of R**X** (1 M) with NaN_3 (1.1 eq.) in DMF at 25°C.

	RX	k (M^{-1} s^{-1})
1.	1-PE**Br***	2.1
2.	Bz**Cl**	$1.5\ 10^{-3}$
3.	E**B***i*B	$7.2\ 10^{-4}$
4.	M**Cl**P	$4.3\ 10^{-4}$
5.	2-**Cl**PN	$7.6\ 10^{-5}$
6.	1-PE**Cl**	$6.7\ 10^{-5}$

*0.02 M in DMF

ments confirmed the large difference in rate constants between the chlorinated and brominated substrates (Table 2, experiments #1 and #2 were analyzed by GC, #3 and #4 by ^{1}H-NMR). When 1-phenylethyl bromide was mixed in a 1/1 ratio with 1-phenylethyl chloride (#1) or with methyl 2-chloropropionate (#2) and sodium azide was added (1 eq. towards 1-PEBr), 1-phenylethyl bromide reacted selectively with the azide. When 1-phenylethyl bromide was mixed with methyl chloroacetate (#3), a 50/50 mixture of the corresponding azides was obtained. When 1-phenylethyl bromide was mixed with benzyl chloride (#4), 18% of the benzyl chloride was converted to the azide. The latter result suggested that benzyl chloride reacted approximately 4.5 times slower than 1-phenylethyl bromide, the rate constant for 1-phenylethyl bromide being $k = 6.75\ 10^{-3}\ M^{-1}\ s^{-1}$. However, when the concentrations of 1-phenylethyl bro-

TABLE 2. Competition Experiments: Substrate 1 and 2 (1/1 Ratio) were Dissolved in DMF and Sodium Azide (1 eq. towards Substrate 1) was Added. After the Reaction at 25°C, the Reaction Mixture was Analyzed by GC (#1, #2) or ^{1}H-NMR (#3, #4).

	Substrate **1**	Substrate **2**	**Result**
#1	Me-CH(Ph)-Cl	Me-CH(Ph)-Br	Me-CH(Ph)-Br reacts selectively
#2	Me-CH(CO_2Me)-Cl	Me-CH(Ph)-Br	Me-CH(Ph)-Br reacts selectively
#3	MeO_2C-CH_2-Cl	Me-CH(Ph)-Br	**1** → -N_3 : 50% **2** → -N_3 : 50%
#4	C_6H_5-CH_2-Cl	Me-CH(Ph)-Br	**1** → -N_3 : 18% **2** → -N_3 : 82%

mide and sodium azide were lowered to 0.02 M in DMF, and the rate constant was measured directly, a value k = 2.1 M^{-1} s^{-1} was obtained (Table 1). The discrepancy between these two values is presumably due to two factors. First and most important, the direct measurement of the rate constant of 1-phenylethyl bromide was performed in a more dilute solution which favored the formation of more reactive free anions. Therefore, the value k = 2.1 M^{-1} s^{-1} should not be compared with rate constants obtained for substrates at 1 M concentration in DMF. Secondly, during the course of the competitive reaction, benzyl chloride can be converted to benzyl bromide which reacts very fast with the azide, resulting in an underestimated rate constant k = 6.75 10^{-3} M^{-1} s^{-1}.

In order to assure that in all the substitution reactions described the desired products were obtained without any occurrence of side reactions, ^{1}H-NMR of all reaction mixtures were recorded. Table 3 summarizes the data. In none of the cases, formation of side products was observed, the corresponding azide compounds were quantitatively (≥ 97%) formed. This result confirms the excellent nucleophilicity of the azide anion in combination with its low basicity.

Extrapolating the data obtained for the model studies to the polymer compounds, the bromine terminated polymers were expected to be good substrates for nucleophilic displacement reactions. Chlorine terminated polystyrene, polyacrylate or polymethacrylate were expected to react slower. In this context, it is also important to mention that the concentration of the polymer end groups

TABLE 3. ^{1}H-NMR Data for the Model Compounds (r.m. = Reaction Mixture)

Substrate	Solvent	Me- (ppm)	-CH- (ppm)	$-CO_2Me$ (ppm)	-Ph (ppm)
Me-CH(COOMe)-Br	$CDCl_3$	1.85	4.38	3.79	-
Me-CH(COOMe)-Cl	DMSO	1.60	4.70	3.72	-
Me-CH(COOMe)-N_3	r.m., $CDCl_3$	1.45	3.95	3.75	-
Me-CH(Ph)-Br	$CDCl_3$	2.05	5.21	-	7.3
Me-CH(Ph)-Cl	DMSO	1.95	5.10	-	7.4
Me-CH(Ph)-N_3	r.m., $CDCl_3$	1.60	4.68	-	7.4
Me-CH(CN)-Br	$CDCl_3$	2.03	4.39	-	
Me-CH(CN)-Cl	$CDCl_3$	1.88	4.53	-	
Me-CH(CN)-N_3	r.m., $CDCl_3$	1.57	4.33	-	
		2 x Me (ppm)	$-CH_2-$ (ppm)	$-CH_3$ (ppm)	
$(Me)_2C(COOCH_2CH_3)$-Br	$CDCl_3$	1.93	4.25	1.32	
$(Me)_2C(COOCH_2CH_3)$-N_3	r.m., $CDCl_3$	1.48	4.25	1.32	

and thus the substrate concentration is low, compared to the substrate concentration used in the model reactions.

Low molecular weight polystyrene, poly(methyl acrylate) and poly(methyl methacrylate) with halogen end groups were prepared using ATRP. Monomer, CuBr, 2,2'-dipyridyl and solvent were mixed, degassed and after adding initiator, polymerization occurred at 90°C for the acrylates and 110°C for styrene. The obtained polymers are listed in Table 4.

Polystyrene-Br as well as poly(methyl acrylate)-Br (pMA-Br) were reacted in DMF (0.05 M substrate concentration) with sodium azide (1.1 eq.) at room temperature. In both cases, complete substitution of the bromine by the azide end group was observed by ^{1}H-NMR after 1 hour. For polystyrene, the methine proton of the end group -C**H**(Ph)-X was shifted from 4.4 ppm (X=Br) to 4.0 ppm ($X=N_3$). For poly(methyl acrylate), the signal of the methine proton shifted upfield from 4.3 ppm (-C**H**(COOMe)-Br) to 3.9 ppm (-C**H**(COOMe)-N_3). When poly(methyl methacrylate) (pMMA-Br) was reacted under the same reaction conditions, the reaction progressed slowly. After 12 hours, 40% conversion was obtained. However, with a 10-fold excess of sodium azide, complete conversion was obtained after 12 hours. The azide content in pMMA was quantified using a calibration curve made for FT-IR ($y = 1.4\ 10^{-3} + 2.2\ x$; y being the ratio of integration N_3/CO and x being the molar ratio N_3/CO) that was based on the ratio of the integrations of the two peaks assigned respectively to the azide (2112 cm^{-1}) and to the carbonyl groups (1735 cm^{-1}). ^{1}H-NMR indicated that the substitution had occurred without side reactions such as elimination.

For further characterization of the azide end functionalized polymers, Matrix Assisted Laser Desorption Ionization, Time-of-Flight Mass Spectrometry (MALDI-TOFMS) was used. This mass spectrometry technique has been shown to serve as a very useful tool in the elucidation of polymer end groups [16-17]. As example, the MALDI-TOFMS spectrum of azide end functionalized poly(methyl acrylate) is shown in Figure 4. The obtained mass values in the

TABLE 4. Low Molecular Weight Polymers Synthesized by ATRP and Used for Functionalization Reactions

Polymer	GPC-data
Polystyrene-Br	M_n=1370, M_w=1600, M_w/M_n =1.17
Poly(methyl acrylate)-Br	M_n=1850, M_w=2025, M_w/M_n =1.09
Poly(methyl methacrylate)-Br	M_n=1770, M_w=2270, M_w/M_n =1.28

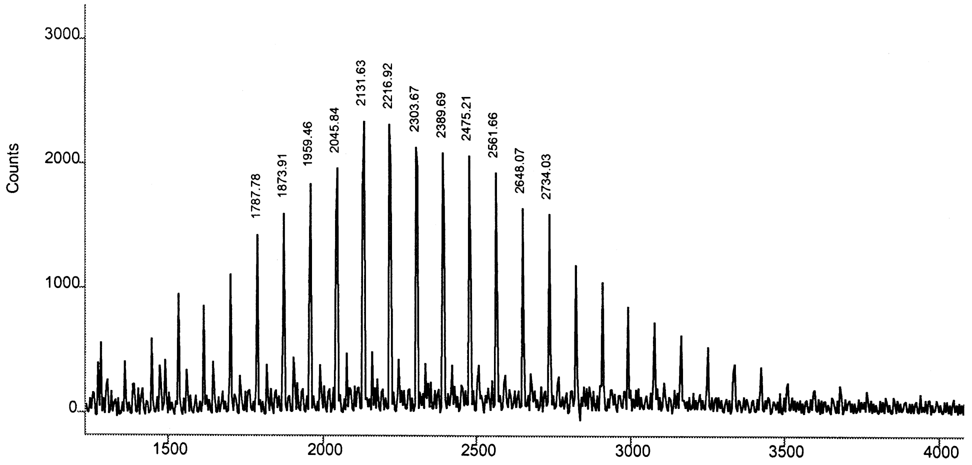


Figure 4. MALDI-TOFMS spectrum of pMA-N_3 (matrix = trans-3-indole acrylic acid doped with Na^+).

spectrum were comparable in an error range of +/-3 a.m.u. with the theoretical mass of pMA-N_3, m = [87($CH_3CH(COOMe)$-) + n x 86 (-$CH_2CH(COOMe)$-) + 42 (-N_3) + 23 (Na)$]^+$. Small peaks due to the loss of N_2, N_3 and presumably N_3 + CH_3 during mass spectrometry were also observed.

CONCLUSION

Polymers synthesized by ATRP have well-defined chlorine or bromine end groups. The reactivity of these halogen end groups of different polymers was studied. Compounds such as 1-phenylethyl halide, methyl 2-halopropionate, ethyl 2-bromoisobutyrate and 2-halopropionitrile were used as models for the end groups of respectively polystyrenes, polyacrylates, polymethacrylates and polyacrylonitrile. According to the model reactions of these compounds with sodium azide, the displacement of the halogen end group by azide in dimethylformamide is a very efficient method to obtain azide end functionalized polymers. The reaction proceeds fast, especially when the leaving group is bromine and the selectivity of the reaction approaches 100%. Bromine end functionalized polystyrene as well as polyacrylate were efficiently converted to azide end functionalized polymer. Bromine terminated pMMA reacted slower under the same reaction conditions. However, with a 10-fold excess of sodium azide, complete conversion was obtained within 12 hours at room temperature.

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